Tetrahedron Letters 54 (2013) 3085–3087

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel, two-step synthesis of 4-pyridone-3-carboxamides from 2-cyano-4-pyrones

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ARTICLE INFO

Article history:
Received 9 February 2013
Revised 11 March 2013
Accepted 28 March 2013
Available online 12 April 2013

Keywords:
2-Cyano-4-pyrones
5-Amino-3-oxopent-4-enamides
4-Pyridone-3-carboxamides
DMF-DMA
Cyclization

ABSTRACT

Reactions of 2-cyano-6-(trifluoromethyl)-4-pyrone, 2-cyano-4-pyrone, and 2-cyano-6-methyl-4-pyrone with aliphatic and aromatic amines in ethanol at −20 °C for 2–21 days gave 5-amino-3-oxopent-4-enamides in 28–78% yields, which were cyclized with DMF-DMA in toluene under ambient conditions to afford 4-pyridone-3-carboxamides in 31–70% yields.

4-Pyridone-3-carboxamides belong to an important class of nitrogen-containing heterocyclic compounds with a broad spectrum of biological activities. Many of their derivatives are selective CB2 cannabinoid receptor ligands,[1] and possess herbicidal[2] and anti-inflammatory[3] activities. These heterocyclic amides also exhibit properties of plant growth regulators[4] and are the key frameworks of some natural products (e.g., aspernigrine A and pestalamides B and C[5]) (Fig. 1).

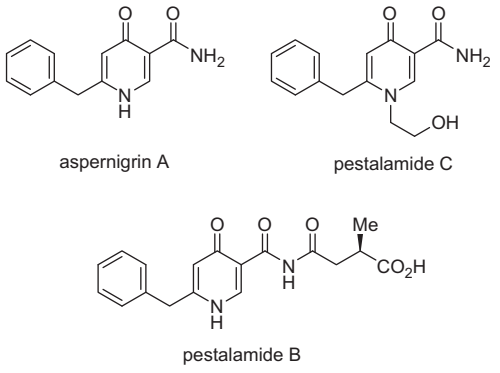

Figure 1. Examples of natural compounds containing a 4-pyridone-3-carboxamide framework.

Reported synthetic methods for the preparation of 4-pyridone-3-carboxamides are based on the reactions of 4-pyrone-3-carboxylic acid derivatives with amines (transformation of the 4-pyrone ring into a 4-pyridone ring),[1,4] the treatment of α-acylated enaminoamides with *N*,*N*-dimethylamide dimethyl acetals,[4b,c] the reaction of 3-aminoacrylic acid derivatives with 2,2,6-trimethyl-1,3-dioxin-4-one[4] or diketene,[3] the transformation of 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone) into 4-pyridone-3-carboxylic acid derivatives,[1] as well as the self-condensation of *N*-aryl acetoacetamides mediated by sodium persulfate[5b] or *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of water.[3] In this Letter, we report a novel synthesis of 4-pyridone-3-carboxamides from 5-amino-3-oxopent-4-enamides, which in turn were prepared from the corresponding 2-cyano-4-pyrones.

We previously found[6] that dehydration of 4-*oxo*-6-(trifluoromethyl)-4*H*-pyran-2-carboxamide (**1a**)[7] with trifluoroacetic anhydride in the presence of pyridine at 0 °C led to the formation of 2-cyano-6-(trifluoromethyl)-4-pyrone (**2a**) in 61% yield. We now report the synthesis of 2-cyano-4-pyrone (**2b**) and 2-cyano-6-methyl-4-pyrone (**2c**) from the corresponding 4-pyrone-2-carboxamides **1b**,**c** under the same conditions, in 48%[8] and 55% yields, respectively (it proved important to carry out the reaction at −10 °C). Surprisingly, as in the case of **1a** and **2a**, the isolation and characterization of which had not been reported prior to our work,[6,7] none of these simple 2-cyano- and 2-carbamoyl-4-pyrones had been recorded in the literature (Scheme 1).

Pyrone **2a**, due to activation of the conjugated system by two electron-withdrawing groups (CF_3 and CN), is a highly electrophilic

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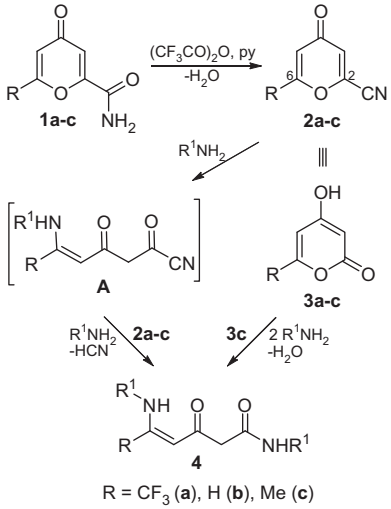
0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.03.132



Scheme 1. Synthesis of 5-amino-3-oxopent-4-enamides **4**.

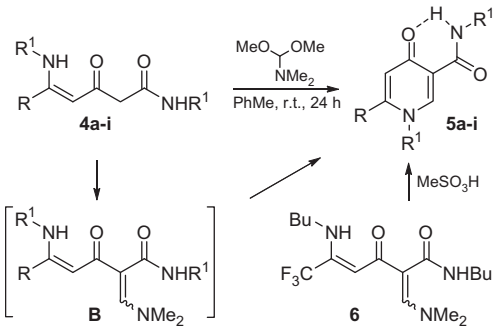
substrate, which is able to react with different nucleophiles with or without affecting the pyrone ring.[6] We found that **2a** reacted easily with both aliphatic and aromatic amines in ethanol at −20 °C over 2 days to produce CF_3-containing 5-amino-3-oxopent-4-enamides **4a**–**f** in yields of 28–78%. The first step of the reaction leading to **4** presumably involves attack of the NH_2 group at C-6 of **2a** with concomitant opening of the pyrone ring to give intermediate **A**, which is a reactive acyl cyanide. Subsequent substitution of the cyano group adjacent to the carbonyl group occurs by the action of a second amine molecule and leads to the carbamoylated aminoenones **4**. This reaction reveals the high reactivity of the pyrone ring of **2a** in contrast to the pyrone ring of 2-cyano-4-pyrone (**2b**), which reacted with benzylamine and *p*-anisidine at −20 °C over 8 days to give aminoenones **4g**,**h** in good yields (49–62%). The less reactive 2-cyano-6-methyl-4-pyrone (**2c**) reacted under the same conditions only with benzylamine, over 3 weeks, to produce compound **4i** in 50% yield, which has been previously obtained from triacetic acid lactone (**3c**) and benzylamine[9] (Scheme 1 and Table 1). Thus, 2-cyano-4-pyrones **2** can be considered as synthetic equivalents of 4-hydroxy-2-pyrones **3**, of which 4-hydroxy-6-(trifluoromethyl)-2-pyrone (**3a**) and 4-hydroxy-6-methyl-2-pyrone (**3c**) are known compounds.[10]

5-Amino-3-*oxo*-4-enamides **4** belong to a poorly explored class of polyfunctional compounds, the chemical properties of which have still not been investigated (besides acid hydrolysis to 4-hydroxy-2-pyridones[6,9]). In connection with this, we examined the reactivity of carbamoylated aminoenones **4** to construct biologically interesting CF_3-containing 4-pyridone-3-carboxamides as well as non-fluorinated pyridones. We reasoned that reaction of

Table 1
Yields and melting points of amides **4** and pyridones **5**

R	R^1	Amide	Yield (%)	mp (°C)	Pyridone	Yield (%)	mp (°C)
CF_3	Me	**4a**	37	104–105	**5a**	64	175–176
CF_3	Ph	**4b**	78	108–109	**5b**	60	161–162
CF_3	2-$MeOC_6H_4$	**4c**	59	119–120	**5c**	62	212–213
CF_3	4-$MeOC_6H_4$	**4d**	58	131–132	**5d**	68	182–183
CF_3	4-BrC_6H_4	**4e**	28	187–188	**5e**	31	241–242
CF_3	*n*-Bu	**4f**	76	65–66	**5f**	56[a]	liq.
H	$PhCH_2$	**4g**	62	113–114	**5g**	54	129–130
H	4-$MeOC_6H_4$	**4h**	49	152–153	**5h**	70	201–202
Me	$PhCH_2$	**4i**	50	107–108[b]	**5i**	58	163–164

[a] From **6**.
[b] mp 106–108 °C (Ref.13).



Scheme 2. Synthesis of 4-pyridone-3-carboxamides **5**.

DMF-DMA with an appropriately substituted amide **4** would provide the desired 4-pyridones. During the optimization studies, it was found that treatment of compounds **4a**–**i** with DMF-DMA in toluene under ambient conditions for 24 h gave 4-pyridone-3-carboxamides **5a**–**i** in 31–70% yields.[11,12] The mechanism of the reaction involves α-enamination of **4** with DMF-DMA to give intermediate **B**, which then undergoes cyclization to afford 4-pyridone-3-carboxamides **5**. Indeed, in the case of *N*,*N*′-dibutyl substituted amide **4f**, intermediate acyclic product **6** was isolated as a single isomer in 65% yield. The latter was converted into the corresponding 4-pyridone **5f** by treatment with methanesulfonic acid in toluene at room temperature over 0.5 h (Scheme 2 and Table 1).

Although the chemistry of 4-pyridones has been well documented,[1–5] compounds **5** are hitherto unreported. This new cyclization process allows the preparation of a variety of 4-pyridone-3-carboxamides **5** with substituents on the amide and ring nitrogen atoms, and proves that the methylene component of the β-ketoamide moiety is more reactive to DMF-DMA than the methylene component of the aminoenone moiety.

The structures of all the compounds were established from their elemental analyses and spectral (^1H, ^{13}C NMR, and IR) data. In the ^1H NMR spectra of pyridones **5**, protons H-2 and H-5 appeared as superfluous 0 singlets at δ 8.37–8.67 and δ 5.63–7.26, respectively (doublets for **5g**,**h**, ^3J = 7.4 Hz, ^4J = 2.2 Hz). Another characteristic feature was the appearance of the NH signal in the range of δ 9.8–12.5, indicating that there is intramolecular hydrogen bonding in **5**.[3] In the ^{13}C NMR spectrum of **5d**, three characteristic quartets due to the CF_3 (δ 119.3, $^1J_{C,F}$ = 275.0 Hz), C-5 (δ 119.9, $^3J_{C,F}$ = 4.2 Hz), and C-6 (δ 138.2, $^2J_{C,F}$ = 33.5 Hz) carbons were observed, additionally confirming the 4-pyridone structure.

In summary, we have developed a simple two-step synthesis of potentially biologically active 4-pyridone-3-carboxamides, including CF_3-containing derivatives, which involves the preparation of 5-amino-3-oxopent-4-enamides via the reaction of 2-cyano-4-pyrones with amines, and their subsequent cyclization under the action of DMF-DMA.

Acknowledgment

This work was supported by the Ural Federal University (Program of Support of Young Scientists).

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8. *2-Cyano-4-pyrone (**2b**).* Yield 50 mg (48%), yellowish crystals, mp 89–90 °C (toluene). IR (ATR) 1705, 1621, 1599, 1502, 1483, 1474 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.53 (1H, dd, J = 6.0, 2.6 Hz, H-5), 7.32 (1H, d, J = 2.6 Hz, H-3), 8.26 (1H, d, J = 6.0 Hz, H-6). Anal. Calcd for $C_6H_3NO_2$: C, 59.51; H, 2.50; N, 11.57. Found: C, 59.41; H, 2.37; N, 11.11.
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11. *General procedure for the preparation of pyridones **5**.* Amide **4** (0.14 mmol) was added to a solution of DMF-DMA (27 mg, 0.28 mmol) in toluene (2 mL). The reaction mixture was stirred in toluene under ambient conditions for 24 h, then the solvent was removed and the residue recrystallized from an appropriate solvent.
12. *N,1-Bis(4-methoxyphenyl)-4-oxo-6-(trifluoromethyl)-1,4-dihydropyridine-3-carboxamide (**5d**).* This compound was obtained from **4d** as a colorless solid, yield 35 mg (68%), mp 182–183 °C (EtOH). IR (ATR) 3080, 3000, 1679, 1611, 1578, 1508 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 3.74 (3H, s, MeO), 3.85 (3H, s, MeO), 6.94 (2H, d, J = 9.0 Hz, Ar), 7.12 (2H, d, J = 9.0 Hz, Ar), 7.20 (1H, s, H-5), 7.61 (2H, d, J = 9.0 Hz, Ar), 7.64 (2H, d, J = 9.0 Hz, Ar), 8.37 (1H, s, H-2), 12.00 (1H, s, NH); ^{19}F NMR (376.5 MHz, DMSO-d_6, C_6F_6) δ 101.9 (s, CF_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.2, 55.6, 114.2, 114.4, 118.9, 119.3 (CF_3, q, $^1J_{C,F}$ = 275.0 Hz), 119.9 (q, $^3J_{C,F}$ = 4.2 Hz), 121.2, 128.8, 131.1, 132.7, 138.2 (q, $^2J_{C,F}$ = 33.5 Hz), 149.2, 155.8, 160.2, 160.4, 176.3. Anal. Calcd for $C_{21}H_{17}F_3N_2O_4$: C, 60.29; H, 4.10; N, 6.70. Found: C, 60.40; H, 4.28; N, 6.82. *N,1-Bis(4-methoxyphenyl)-4-oxo-1,4-dihydropyridine-3-carboxamide (**5h**).* This compound was obtained from **4h** as a colorless solid, yield 29 mg (70%), mp 201–202 °C (PhMe). ^1H NMR (400 MHz, DMSO-d_6) δ 3.75 (3H, s, MeO), 3.84 (3H, s, MeO), 6.65 (1H, d, J = 7.4 Hz, H-5), 6.88 (2H, d, J = 8.9 Hz, Ar), 7.14 (2H, d, J = 8.9 Hz, Ar), 7.62 (4H, m, Ar), 8.17 (1H, dd, J = 8.9, 2.4 Hz, H-6), 8.62 (1H, d, J = 2.4 Hz, H-2), 12.50 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.2, 55.6, 114.2, 115.0, 118.5, 119.9, 121.1, 124.8, 131.6, 135.9, 141.3, 143.9, 155.5, 159.4, 161.3, 176.7. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.70; H, 5.20; N, 8.02.
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